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Opioid Induced Constipation

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1. Introduction

The prevalence of chronic pain in the adult population ranges from2 to 40 (1–3). The chronic use of opioids for the treatment of non-cancer pain is commonly encountered in clinical practice.

The American Society of the Interventional Pain Physicians has issued guidelines for appropriate use of opioids (4).

With the increased use of opioids, there are more patients presenting with opioid induced constipation (OIC) or opioid bowel dysfunction (OBD) (5,6).

The definitions of constipation include a reference to infrequent, difficult or incomplete bowel evacuation that may lead to pain and discomfort; with stools that can range from small, hard 'rocks', to a large bulky mass. Constipation may be debilitating among those who require chronic analgesia (7); OIC or OBD affected an average of 41 % patients taking an oral opioid for up to 8 weeks in a meta-analysis of 11 placebo-controlled, randomized studies in non-malignant pain (14). In a survey of patients taking opioid therapy for pain of non-cancer origin, who required laxative therapy, only 46 % of opioid-treated patients reported achieving the desired treatment results > 50 % of the time, in contrast to the reported satisfaction in 84 % of control subjects (8).

The prevalence of constipation was 46.9 % and chronic abdominal pain 58.2 % among 100 ambulatory patients with moderate-to-severe chronic non-cancer pain.

In the United States and European survey of 322 patients taking daily oral opioids and laxatives, 45 % of patients reported < 3 bowel movements per week, 81 % reported constipation, and 58 % straining, symptoms were most oft en reported as severe, had at least a moderate negative impact on overall quality of life and activities of daily living. The objectives of this narrative review are to summarize essential aspects of the epidemiology of opiate-induced constipation (OIC), summarize the effects of opiates on gastrointestinal functions that lead to constipation, evaluate pharmacological approaches to treat or prevent OIC.

2. Pathophysiology of opioid induced constipation

The opioid receptors identified as having effects on human gastrointestinal function are δ -, κ -, and μ -receptors. They all belong to the family of G-protein-coupled receptors, and

inhibit adenylate cyclase. The m-receptors are the principal mediators of the analgesic action of endogenous and exogenous opioids as well as of the major side-effects, ie, sedation, bowel dysfunction, respiratory depression, and dependence. At the membrane level, they reduce neuronal excitability and neurotransmitter (acetylcholine) release (9) with an overall inhibitory effect on the neuron.

Opioid receptors are widely distributed in the central and peripheral nervous system, the intestinal musculature, and other tissues. In the gastrointestinal tract, μ-receptors are widely distributed in the submucosa (10), as well as in the ileal mucosa. They influence ion transport changes (11). While μ – and κ -opiate receptors are more representative in stomach and proximal colon (12).

The cause of constipation in opiate users is multi-factorial (13). Opioids interfere with normal gastrointestinal motility by delaying transit, stimulating non-propulsive motility, segmentation and tone, and stimulation of sphincters such as the pylorus and ileocecal sphincter (13) through their effects on enteric neurons (14). They can also stimulate the absorption of fluids, mainly by delayed transit, and by stimulating mucosal sensory receptors that activate a reflex arc that facilitates further fluid absorption (15,16). These multiple effects lead to OIC.

3. Pharmacological approach to OIC

3.1 μ-opioid receptor agonists

Tapentadol

Tapentadol HCI is a μ -opioid agonist that also inhibits norepinephrine reuptake (17). The analgesic effect is so a combination of two different mechanism. In different trials norepinephrine reuptake inhibition (e.g., with venlafaxine (18) and the α 2-adrenergic agonist clonidine (19, 20) are associated with reduced colonic or rectal sensation in response to distension. Moreover it seems that, because of the combined analgesic action of tapentadol , the pain control can be achieved with a relatively lower level of μ-opioid agonism, which therefore reduces the gastrointestinal adverse effects such as constipation. As an analgesic tapentadol has a more favorable gastrointestinal side-effect profile than the classic μ-opioid receptor agonist oxycodone (21).

However, there were substantially lower incidences of gastrointestinal-related adverse effects with tapentadol extended release than with oxycodone controlled release (22). Similarly, tapentadol extended release, 100– 250 mg b.i.d., effectively relieved moderate-to-severe chronic low back pain over 15 weeks with a better gastrointestinal tolerability than oxycodone HCl controlled release, 20 – 50 mg b.i.d. (23). Studies of the pharmacodynamic effects of tapentadol on gastric emptying and colonic transit would be of significant interest.

3.2 μ-opioid receptor antagonists

The main problem in using opioid antagonist for reversing the gastrointestinal adverse effects of opioid that the dose efficaciousness in reversing OIC may inhibit the analgesic effect of opioids, causing either opiate withdrawal symptoms or reversal of desirable analgesia.

Naloxone

Naloxone is a competitive antagonist at opioid receptors with much greater affinity for µ - than for κ - or δ -receptors. Naloxone blocks opioid intestinal receptors and has low systemic bioavailability (2%) due to a marked hepatic first-pass effect. In patients with chronic pain, oral naloxone improved symptoms of laxation (24), but because of its very narrow therapeutic index, doses that reverse gut symptoms can often cause reversal of analgesia (25). However, there has been a resurgence of interest in naloxone in a prolonged-release preparation, which shows evidence of analgesic efficacy and safety when used in combination with oxycodone (prolonged release) for moderate-to-severe chronic pain (26) and improved bowel function when compared with oral oxycodone (prolonged release) alone (27). This effiacy continues for up to 52 weeks in patients with non-cancer chronic pain (28).

Naltrexone extended release

There one open-label study that evaluated the safety of a combination of extended-release pellets of morphine sulfate with a sequestered naltrexone core (administered once or twice daily) in patients with chronic, moderate to-severe pain. The pain-relieving objectives of treatment were achieved using dosages of the combination that could be adjusted in accordance with the investigator' s best medical judgment. The median average daily dose of morphine over the course of study in the safety population was 58.6 mg. 465 patients received one or more doses, 160 completed the 12-month study: 30% of the discontinuations occurred in the first month, most often because of adverse events (23.7 %), nausea (5.4 %), constipation in (3.4 %), and vomiting in (2.6 %). Most of the 465 patients (81.3 %) experienced one or more adverse events, most commonly constipation (31.8%) or nausea (25.2%). Opiate withdrawal symptoms were mild and affected < 5% of patients during each week of the study (29). Form these data the authors concluded that combination does not resolve OBD.

3.3 Association of opioid agonist and antagonist

Oxycodone/Naloxone

A new oral formulation (oxycodone/naloxone, OXN) that combines prolonged-release oxycodone (PRO) and prolonged-release naloxone (PRN) was devel- oped. The ratio of 2:1 PRO to PRN was chosen for the new tablets, which have different strengths: 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg [30,31]. The aim of this formulation is to counteract opioid-induced con- stipation (OIC) development [32] through naloxone local antagonist effect on the opioid receptors in the gut wall [33] while maintain analgesia [35] due to the high systemic oxycodone availability after oral ad- ministration (60–87%)

Meissner et al. [30] reported a randomized, double- blind study that assessed analgesic efficacy and, impact on the OIC of OXN and identified the optimal dose ratio of oxycodone and naloxone. Two hundred and two patients with chronic pain (most non-malignant, 2.5% cancer-related pain) and stable oxycodone dose (40, 60 or 80 mg per day) were randomized into groups that received 10, 20, and 40 mg per day naloxone or placebo. After 4 weeks of the maintenance phase, patients received oxycodone for two weeks. Pain intensity was evaluated by the NRS, and bowel function was assessed by the bowel function index (BFI). No loss of analgesia with naloxone was observed. Na- loxone at doses of 20 and 40 mg improved bowel

function in comparison to placebo (p < 0.05). The combination was well tolerated with no unexpected adverse effects. A trend towards an increase in diarrhea with the higher naloxone doses was observed. The 2:1 oxyco- done/naloxone ratio was identified as the most suitable.

3.4 Peripherally restricted μ- opiate receptor antagonists

Methylnaltrexone

Methylnaltrexone is a quaternary ammonium derivative of naltrexone, an opioid antagonist similar to naloxone, but it is less lipid soluble, so, less likely to cross the blood–brain barrier (36). Methylnaltrexone blocks acute morphine-induced delay in orocecal transit time without affecting analgesia or causing central opiate withdrawal symptoms.

Intravenous methylnaltrexone infusion reversed methadone induced constipation, increasing stool frequency and decreasing orocecal transit times (37,38). Orally administered methylnaltrexone showed the same results (39) with plasma drug levels were very low, suggesting a local site of action in the gut.

Several studies evaluated the effect of methylnaltrexone on apin and OIC. Methylnaltrexone, 0.45 mg / kg intravenously (i.v.), reversed the effects of 0.05 and 0.1 mg/kg morphine on orocecal transit in healthy volunteers (40)

Methylnaltrexone (at a dose of 0.15 mg / kg subcutaneously (s.c.), every other day for 2 weeks) was tested for OIC in advanced illness in 133 patients who had received opioids for 2 or more weeks and had received stable doses of opioids and laxatives for 3 or more days without relief of OIC (41). Methylnaltrexone s.c. has been approved by the US Food and Drug Administration, Health Canada and the European Medicines Agency (42). The approved indication is OIC in patients with advanced illness receiving palliative care after failing laxative therapy, and the usual dosing schedule is 1 dose every other day, as needed, but no more frequently than 1 dose in a 24-h period. The recommended dose of methylnaltrexone is 8 mg for patients weighing 38– 62 kg or 12 mg for patients weighing 62 – 114 kg. Patients whose weight falls outside of these ranges should be dosed at 0.15 mg / kg (43).

Alvimopan

Alvimopan is an orally administered, peripherally acting μ -opioid receptor antagonist that does not cross the blood – brain barrier at clinically relevant dosages (44) and does not reverse analgesia or cause opioid withdrawal symptoms. At the moment, Alvimopan is not approved for treatment of OIC. However, there is already significant literature about its potential in OIC associated with chronic opioid therapy.

In a study of 522 subjects reporting < 3 spontaneous bowel movements (SBMs) per week and a pain treatment with ≥ 30 mg oral morphine equivalent unit / day, were evaluated the efficacy of alvimapan on OIC. (45) Participants were randomized to receive alvimopan, 0.5 mg b.i.d., 1 mg once daily, 1 mg b.i.d., or placebo for 6 weeks (45). There was a significant increase in mean SBM / week over the initial 3 weeks of treatment with all 3 doses of alvimopan tested, as well as improvements in straining, stool consistency, incomplete evacuation, abdominal bloating/discomfort, and decreased appetite, which were sustained over 6 weeks. The most frequent adverse events were abdominal pain, nausea, and diarrhea, occurring more frequently in the higher dosage groups. The alvimopan 0.5 mg b.i.d. dose

demonstrated the best benefit-to-risk profile for managing OBD, with a side-effect profile similar to that of placebo (45). There was no evidence of opioid analgesia antagonism.

NKTR-118

NKTR-118 is an oral PEGylated naloxol conjugate that blocks peripheral μ -opioid receptors in the gut. PEGylation of naloxone alters its distribution, reducing central nervous system penetration and metabolism (reduced first-pass effect) while retaining its opioid antagonist properties peripherally (46).

In human pharmacodynamic studies, NKTR-118 normalized morphine-induced delay in orocecal transit (47), while central effects were maintained with uninhibited pupillary constriction.

In a phase 2, placebo-controlled clinical trial of NKTR-118 in OIC patients (< 3 SBM/ week, on a stable opioid dose of 30– 1,000 morphine-equivalent unit / day for ≥ 2 weeks), 208 patients were randomized into three sequential cohorts of 5, 25, or 50 mg for 4 consecutive weeks aft er a 1-week placebo run-in phase. Patients receiving 25 mg or 50 mg (but not 5 mg) NKTR-118 had significantly increased (over baseline) number of SBM during the first week of treatment (primary end point) and over the 28-day treatment period, compared with placebo. There was no evidence of opioid withdrawal, reversal of analgesia, or increase in opioid use at any dose tested. Most frequent side eff ects were abdominal cramping, diarrhea, nausea, and vomiting, which were more frequent in the 50 mg cohort. *TD-1211* TD-1211 is an orally administered, peripherally selective, multivalent inhibitor of the μ - opioid receptor. It has high affinity for human μ - and δ -receptors, and guinea-pig μ -opioid receptors, with > 6,000-fold selectivity for the μ –opioid receptor over non-opioid receptors, ligand-gated ion channels, enzymes, ion channels (including hERG), and transporters. It inhibits loperamide-induced reduction in gastric emptying and attenuation of castor oil-induced diarrhea following acute oral dosing to conscious rats.

3.5 Prucalopride, a prokinetic 5-HT 4 receptor agonist

Prucalopride is a new, selective 5-HT 4 agonist with efficacy in relief of chronic constipation and safety from a cardiovascular perspective. In a phase 2, double-blind, placebo-controlled study 196 patients with OIC were randomized to receive placebo, prucalopride 2 or 4 mg for 4 weeks. The increase from baseline of ≥ 1 spontaneous complete bowel movements (SCBM) per week (weeks 1 – 4, primary end point) was greater in the prucalopride groups (35.9 % (2 mg) and 40.3% (4 mg) than placebo (23.4%), reaching statistical significance in week 1. Prucalopride, 4 mg, significantly improved patient-rated severity of constipation and effectiveness of treatment vs. placebo, and improved Patient Assessment of Constipation - Symptom (PAC-SYM) total scores and Patient Assessment of Constipation-Quality of Life (PAC-QOL) total and satisfaction subscale scores. The most common adverse events were abdominal pain and nausea.

Lubiprostone

Lubiprostone is a chloride channel activator that induces intestinal secretion.

Lubiprostone, in vitro, stimulates chloride secretion that was suppressed by morphine. *In vivo*, instead, s.c. lubiprostone increased fecal wet weight and numbers of pellets expelled in guinea-pig and mouse (48) reduced by Morphine.

Injection of lubiprostone, 30 min after morphine, reversed morphine-induced suppression of fecal wet weight. The data suggest that lubiprostone, bypasses the neurogenic constipating effects of morphine by directly opening chloride channels in the mucosal epithelium (48).

4. Conclusion

The management of patients with OIC is an increasingly relevant problem with the extensive use of opioids for the relief of chronic pain, often associated with benign conditions. Several novel pharmacological approaches are being developed, including assessment of promotility and secreta- gogue agents that have efficacy in chronic idiopathic constipation. Other approaches are directed at the reversal of peripheral opiate effects in the gut while maintaining the desired analgesic efficacy. Several new approaches are promising, including tapentadol, combination of opioids with prolonged release naloxone, NKTR-118, and TD-1211. An evidence-based management approach for OIC will be more feasible after the new generation of drugs is formally and thoroughly studied in large, high-quality clinical trials.

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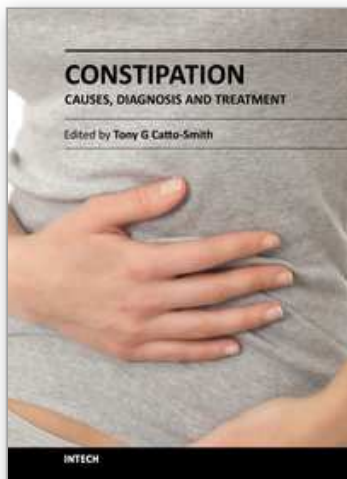
Constipation - Causes, Diagnosis and Treatment

Edited by Dr. Anthony Catto-Smith

Constipation is common in both adults and children. Estimates would suggest a median prevalence of around 12-16% in the general population. While regarded as a minor nuisance in some cases, its consequences can be severe, with a substantial impact on quality of life. Secondary faecal soiling has a profound psychological effect at all ages. This book provides contributions from authors with a range of backgrounds which clarify the pathogenesis, diagnosis, and therapy of constipation for the general population and also for certain high risk groups.

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